IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant: J. Gregor Sutcliffe	Attorney Docket SCRF 32.0 DIV II 3181/58687
Serial No.: 08/116,873	
Filed: September 3, 1993	Group Art Unit 1813
For: SYNTHETIC POLYPEPTIDES CORRESPONDING TO PORTIONS OF PROTEINOIDS TRANSLATED FROM BRAIN-SPECIFIC mRNAs, RECEPTORS, METHODS AND DIAGNOSTICS USING THE SAME	PATENT
Examiner: L. Schriener	

APPELLANT'S BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is an Appeal from the Final Office Action dated July 11, 1995 finally rejecting claims 26-30, 32 and 33.

REAL PARTY IN INTEREST

This application is a division of several earlier applications, two of which have matured into U.S. Patents No. 4,900,811 and No. 5,242,798. The original application and its inventions were assigned to the Scripps Clinic and Research Foundation, of La Jolla, California, now known as the Scripps Research Institute. The Scripps Research Institute is the real party in interest.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF THE CLAIMS

Claims pending: 26-33

Claims rejected: 26-30, 32 and 33

Claims cancelled: 1-25

Claim allowed: 31

Claims on Appeal: 26-30, 32 and 33

A copy of the claims on appeal appears in Appendix I.

STATUS OF THE AMENDMENTS

The last-filed amendments have been entered.

SUMMARY OF THE INVENTION

The invention relates to isolated and purified complementary DNA (cDNA) of a predetermined length of about 500 to about 1800 nucleotide bases. (Page 28, line 9 through page 29, line 36; page 57, line 14 through page 61, line 3. A cDNA of interest is complementary to a cytoplasmic messenger RNA (mRNA) of a mammal. (Page 3, lines 4-9; page 67, lines 4-9, claim 10; and page 17, line 31 through page 18, line 2.) The mRNA is brain-specific; i.e., present only in brain cells, and not in the cells of the liver, kidney, gut, lung, heart or skeletal muscle of a mammal of a mammal of the same species. (Page 14, lines 1-22, page 28, line 32 through page 29, line 2, and page 37, lines 7-9.) The mRNA encodes a proteinoid that is neuroactive. (Claims 4 and 13.)

ISSUES

1. WHETHER REJECTION OF THE CLAIMS ON APPEAL AS BEING VAGUE AND INDEFINITE WAS CORRECT.

2. WHETHER REJECTION OF THE CLAIMS ON APPEAL AS NOT BEING ENABLED WAS CORRECT.

GROUPING OF CLAIMS

The claims stand or fall together.

ARGUMENT

I. THE CLAIMS HAVE THE DEFINITENESS REQUIRED BY THE SECOND PARAGRAPH OF SECTION 112

All of the claims have been rejected as allegedly being vague and indefinite. Several bases are asserted for those conclusions, and those assertions will be dealt with below.

A. Extraneous Explanations Are Not Required

The Action of January 11, 1995 from which this rejection arose asserts that:

> "The claims read on so many DNAs that one cannot determine which DNAs are intended. Moreover, it is not possible for the public to determine from the claims what they comprehend since they require explanations extraneous to both the specification and claims."

It can be agreed that the claims read on a large number of DNAs. Breadth is not, however, indefiniteness. See, for example, In re Gardner et al., 166 USPQ 138 (CCPA 1970).

In regard to "explanations extraneous to both the specifications and claims", no explanation has been provided as to what explanations, extraneous or otherwise, are allegedly required by the claims. Rather, the claims are quite specific in that a claimed DNA complements an mRNA of a mammal, and that mRNA is present in brain cells of that mammal but not in the cells of the liver, kidney, gut, lung, heart or skeletal muscle of that mammal. These mRNAs are referred to as being brain-specific.

See page 14, lines 1-22. A brain-specific DNA also has a neuroactive function.

All of those recitations are in the claims. All of those recitations are supported in the specification as was noted in the Preliminary Amendment filed on October 10, 1994. This basis for rejection should therefore be reversed.

B. A Skilled Worker Would Readily Understand the Claim Language

The Action next quotes from a claim as to the length of the DNA in bases and the nature of that DNA being complementary to a brain-specific mRNA. The Action asserts without any support that the quoted language would not enable a skilled worker to determine the meaning intended by the quoted language. This assertion cannot be agreed with.

DNA length is usually measured by the number of bases in the chain. As a consequence, the recited length limitation is eminently clear to a worker of ordinary skill to whom these claims are directed.

Similarly, that a DNA is complementary to an RNA is the basis for Southern and Northern blotting techniques that are well known in this art and are discussed in the specification. Again, a worker of ordinary skill would have no problem understanding this word, nor with cDNA as is claimed.

Cytoplasmic messenger RNA is what it says it is. That is, mRNA present in the cytoplasm of a cell as compared, for example to the nucleus or mitochondria. A first year biology student, let alone a skilled worker would also have no problem with that phrase.

The presence of the mRNAs in substantially only brain cells has been discussed in the parental applications. The

Board's attention is also invited to page 28, lines 24-29. Here again, no problem in understanding should be encountered by a worker of ordinary skill with this phrase.

This basis for rejection should therefore be reversed.

C. Definition of the Claimed Subject Matter is Clear to Those of Skill In This Art

The Action continued by asserting that the claimed "DNAs have not been defined by structure and the intended functions are unclear." Attention was directed to Ex parte Tanksley, 26 USPQ2d 1384 (BPAI 1991) in which this Board held that the claims must be so definite as to allow their comparison with the available art and also to make it possible to determine from the claims what it is they comprehend.

The first of the Board's holdings appears to be clearly correct, whereas the second does not appear to be the law to the extent that the specification and prosecution file history should also be consulted by the "public" in determining what is comprehended by the claims. [In re Mayhew, 188 USPQ 356, 359 (CCPA 1976); In re Moore & Janoski, 169 USPQ 236, 238 (CCPA 1971)] Nevertheless, it is submitted that the claims here are cast with sufficient clarity so that both tests are readily passed.

As to function of the DNAs, it is clear to a skilled worker that they are complementary to an mRNA that encodes a brain-specific proteinoid. The proteinoid is neuroactive. The function requested is thus asserted in the claims.

The structure of the DNAs need not be recited. The Board in Tanksley noted on reconsideration that one could claim the DNAs there in question by "base sequence...and/or function."

Such a function has been asserted along with several base sequences. No more is needed under Tanksley.

To the question of whether a worker of ordinary skill could understand what is claimed here, one must remember that the present application contains almost all of two published papers that were made of record here and in each of the parent patents. Those two papers are Sutcliffe et al., Cell, 33:671-682 (1993) and Milner and Sutcliffe, Nucleic Acids Res., 11(6):5497-5520 (1983).

The claims are cast in the language of one or both of those papers, and as has been noted before, the words of those claims are readily understood by a worker of ordinary skill in this art. Those papers are so well understood that they have been cited about 380 times in the literature through February 15 of 1995, of which about 280 papers are by one or more authors that do not include Dr. Sutcliffe. That number of citations is clearly indicative of the fact that workers of ordinary skill know and understand what has been claimed here. A two-part photocopy of the printout from a citation search using the Dialog data base is a part of this record as Exhibit 1 to the Amendment mailed on April 11, 1995.

It is thus submitted that not only does that "public" of skilled workers know what is comprehended by these claims, but that these claims can be compared with the prior art. Indeed, the Examiners of two parental patents had little difficulty in comparing the polypeptides of U.S. Patent No. 4,900,911 encoded by a DNA claimed here with the art or the process steps of parental U.S. Patent No. 5,242,798 with the art.

The two tests of Tanksley have thus been passed. There is therefore no basis to limit the claims here only to the

sequences originally disclosed. This rejection should therefore be reversed.

II. THE CLAIMS ON APPEAL ARE ALSO WELL ENABLED UNDER THE FIRST PARAGRAPH OF SECTION 112

The claims on appeal were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The single claim that recites specific sequences, claims 31, was allowed. The Action of January 11, 1995 asserts that the "scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of nucleic acids broadly encompassed by the claims..." and that the number of DNAs claimed is indeterminant.

The enablement requirement as applied here requires that a worker of ordinary skill be able to make and use a cDNA of the claims. The Court has held that the question of enablement revolves around whether the

> "disclosure contains sufficient teaching regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention" [In re Angstadt and Griffen, 190 USPQ 214, 218 (CCPA 1976); emphasis in the original.]

The Angstadt case dealt with a catalyst complex molecule that contained a transition metal cation from one of several Groups of the Periodic Table, an undisclosed "inorganic anion" for the metal cation, and a hexaalkylphosphoramide whose six alkyl groups contained one to thirty carbon atoms in each alkyl group. The metal salt (cation plus anion) was said to be present at 1-4 moles per molecule and the hexaalkylphosphoramide was present at 1-8 moles per molecule complex.

Footnote 2 of Angstadt noted that the Solicitor asserted that the claim read on thousands of compounds including

"any one of at least 50 metal cations combined with any inorganic anion". Actually, "thousands" was a gross underestimate.

For example, there are eight C_1-C_4 alkyl groups; i.e., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl and iso-butyl. So for the hexaalkylphosphoramidates where the alkyl groups are C_1-C_4, there are 8^6 or 262,144 different phosphoramidates, omitting possible chiral isomers. Multiplication by the number of cations, anions and ratios (1-4:1 salt and 1-8:1 hexaalkylphosphoramide per molecule) skyrockets the number of compounds just for that relatively small number of alkyl groups.

According to Noller, Chemistry of Organic Compounds, W.B. Saunders Company, Philadelphia, 1958, page 38, (Exhibit II to the Amendment mailed April 11, 1995) there are over 4 billion C_{30} alkanes alone. Presuming the number of C_{30} alkyl groups is about the same as the number of alkanes, which is a gross undervaluing as there are 15 straight chain C_{30} alkyls alone, the Angstadt formula actually therefore encompassed an astronomical number of separate compounds once all of the anion, cation, alkyl group and ratio permutations encompassed by the claims are taken into account. For example, there would be about $(4 \times 10^9)^6$ or (4096×10^{54}) different C_{30} hexaalkylphosphoramides alone. That number of compounds exceeds any arbitrarily large number that one could pick from the physical world such as the number of atoms in the earth if it were all iron [(mass = about 6×10^{27}g/55.6g/mole) X 6.023×10^{23} atoms/mole = about 6.5×10^{49} atoms] or the more chemically familiar Avagadro's Number of 6.023×10^{23} molecules per mole.

The Angstadt inventors disclosed just 40 examples, with one compound that did not work in their process. The Court there

held that the inventors did not have to make and test every compound in their claims, nor did every compound have to work.

That Court went on to discuss the disclosure that there taught how to make and how to use a claimed catalyst. It continued that if a skilled worker wanted to make another catalyst than those specifically disclosed in the 40 examples that worker could simply follow the disclosure and make a desired catalyst compound. It further pointed out that the catalysis process was not complicated and needed no special conditions nor equipment. The Angstadt claims were found to be enabled despite the amazingly large number of catalysts encompassed.

That Court went further in saying that some "experimentation" was permitted and held that the key phrase was "undue", not "experimentation". Practicing of that invention "would not 'require ingenuity beyond that to be expected of one of ordinary skill in the art' ... ", at 218 (citation omitted). The same should be the case here.

Angstadt dealt with synthetic organic chemistry. The present application deals with biochemistry in that the enzymic syntheses are biochemistry and the inhibition assays also involve biochemistry.

Attention is invited to In re Wands, 8 USPQ2d 1400, 1407 (Fed.Cir. 1988), a case involving monoclonal antibody preparation and screening, biological and biochemical processes that are about as time consuming than the syntheses and assays here. There, the Court found that practitioners of the art were prepared to screen negative hybridomas. A similar finding was made in Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed.Cir. 1986). Those familiar with the hybridoma/monoclonal antibody art know that such preparations and

screenings often involve months to generate antibodies and thousands of assays. Those procedures are nevertheless well known, accepted and routine in the art.

Turning to the present application, the claims here encompass a large number of cDNAs. The specification teaches how to obtain a cDNA of the claims, as well as providing exemplary procedures.

It is submitted that many orders of magnitude fewer cDNAs are encompassed by the present claims than were encompassed by those found enabled in the Angstadt case. The biochemistry here is well known, straightforward and simple but requires effort. No fancy equipment is needed here.

Thus, the number of species encompassed by a claim does not appear to be relevant. Rather, as the Court noted in Angstadt, the question of enablement revolves around whether the worker of ordinary skill is enabled by the disclosure to make and use the invention. The Action, using an unsubstantiated conclusion and a misplaced reliance on Ex parte Maizel, 27 USPQ2d 1662 (BPAI 1993) asserts that such a worker would not be properly enabled. The specification, Dr. Sutcliffe and other skilled workers through their publications that cite, rely-on and copy Dr. Sutcliffe's work disagree, however.

It is also submitted that the situation regarding the remaining, unsequenced clones of the application is analogous to that discussed in In re Wands, above. There, the inventors had prepared about 140 hybridomas, studied four within the claims and deposited one. The Board held the broad genus claims to those hybridomas/antibodies to not be enabled. The Court reversed.

Here, the brain-specific clones of the application such as those of Table III were shown to be within the claims as of

the filing date. Their sequences have been published seriatim as determined over the last decade. Thus, Dr. Sutcliffe has gone further than did Wands et al. in their application and after an application was filed. The generic Wands materials were found to be enabled, and so should the brain-specific cDNAs here.

In determining who is a worker of ordinary skill in this art, it is appropriate to use the standard of Section 103, and determine the level of skill in this art at the time this invention was made. It is submitted that that level of skill was quite high. Thus, the worker of ordinary skill here would hold a Ph.D. or M.D. degree or both, and would have held a post-doctoral position for 2-4 years. That person would be a sole or senior author of at least six published book chapters, invited papers or other papers published in this field in refereed journals, and would be the head of her/his own research group, or would at least have several laboratory technicians, post-docs and/or graduate students reporting to her/him. Such a person would thus be directing, rather than just carrying out, work in this field.

The previously submitted papers (Documents CA, CB and CC of the IDS) provided views of such workers relating to the present invention and its lack of obviousness. Documents DA, DB, DC and DD that were submitted with the Amendment mailed April 11, 1995 further attest to the enablement provided by the before-mentioned Milner and Sutcliffe, and Sutcliffe et al. articles, and thereby to the enablement provided by the present specification that includes the pertinent disclosures of those papers.

The Board's attention is first invited to Cimler et al., J. Biol. Chem., 262:12158-12163 (1987), Document DA. Those authors obtained brain-specific mRNA and prepared cDNA from that

material. (See the Abstract, near the bottom.) Near the right-hand bottom of page 12162, those authors reviewed the Milner and Sutcliffe and Sutcliffe et al. papers and classified their clone, P-57, into the brain-specific cDNAs of these claims; i.e., the Class III materials (Table III herein).

Document DB, Oyler et al., J. Cell. Biol., 109:3039-3052 (1989), describes a brain-specific protein called SNAP-25. Those authors recognized the present contribution in the second full paragraph of page 3040, along with contributions of others in the field. It should be noted that the cited Sutcliffe et al. paper, that is within this specification, has the earliest publication date by two years compared to the other papers as a means "to identify and characterize novel genes and their encoded proteins that are specifically expressed in the nervous system."

The Board's attention is next invited to the review of Document DC, Kato, TINS, 15:319-212 (1992). The paragraphs on page 321 under the heading "Shotgun analysis" are most compelling. The author here credits the Sutcliffe et al. paper included in this application as pioneering this field. That author then concluded the section of the review by stating:

> "Using the methods described above, rare clones of particular interest can be obtained. Unfortunately, a great deal of effort is required to obtain specific clones. However, the goal of making a reasonably large catalogue of cDNAs is readily achievable."

A fourth paper, Document DD, Marechal et al., Anal. Biochem., 208:330-333 (1992) recognized the present contribution (footnote 3 to Milner and Sutcliffe) and disclosed a short cut

involving a hybridization step that removed other than brain-specific clones. Nonetheless, the cDNA clones isolated contained 500 to about 2200 bp and corresponded to mRNAs that were not present in liver, kidney, spleen or intestinal (gut) tissues. Those clones were referred to as being brain-specific. (See the heading at page 332.)

The previous discussion and previously submitted Dialog search printout note that the two papers by Dr. Sutcliffe and his co-workers that are present in this application and whose disclosures form the basis for these claims were cited about 280 times by workers of ordinary skill in this art. Those workers were able to use those disclosures for their own work and arrive at new results.

It is submitted that the evidence provided in this record represents a true assessment that the disclosures of this application are enabling for other than the specific cDNAs whose sequences are disclosed. As Kato pointed out in the before-quoted portion of his review, a worker of ordinary skill can readily prepare a cDNA of these claims even though the work to obtain them requires a great deal of effort.

That great deal of effort is not, however, undue experimentation, a test for enablement. Here, nothing approaching ingenuity beyond that expected of one of ordinary skill in this art is required, and that further ingenuity is what is meant by undue experimentation. In re Angstadt and Griffin, 190 USPQ 219, 218 (CCPA 1976).

Thus, the scope of these clams has been well enabled by the present disclosure, and this rejection should be reversed.

The January 11, 1995 Action also based its rejection in part on the Board's decision in Ex Parte Maizel, analogizing the

fact situation there to the present situation. It is submitted that that comparison is inapt.

The inventors in Maizel found one tree and tried to claim a forest. Dr. Sutcliffe isolated 47 clones of the claims and sequenced four of them as being illustrative. Dr. Sutcliffe planted examples of his complete claims forest. His continuing publications in this field and those of others who have used these teachings have provided growth to those plantings.

The cDNAs of these claims are more akin to the catalyst molecules of Angstadt than to the single means of Maizel. Angstadt's forty examples including one that did not work represent a smaller percentage relative to the breadth of the claims there than do the 47 isolated clones or the four clones sequenced here.

The analogy to Maizel also breaks down here because there is no analogous "means" here, stated or otherwise, as there was in Maizel. The claims do not recite biological equivalents.

The parallel with Maizel fails further because that case rested on In re Fisher, 166 USPQ 18, 24 (CCPA 1970) in which claims were drafted to a polypeptide of a length that could not have been built at the time the Fisher application was filed, as Nobel Laureate Merrifield's work on peptide synthesis had not been published. Fisher never demonstrated ability to prepare his peptide. Here all of the tools were in place and Dr. Sutcliffe and his group, and others, have been working since 1983 watering, fertilizing and growing his forest in paper after paper that detail their findings with their brain-specific cDNAs. A complete set of those papers in addition to those already provided was offered, but not accepted by the Examiner. Those papers are not included here simply to keep the file smaller.

It is thus submitted that these claims are well enabled by the application itself as well as by the unsolicited statements of others of skill in his art and by Dr. Sutcliffe's continuing work. This rejection should therefore be reversed.

The Final Action dated July 11, 1995 asserts that an infringer could not know if a contemplated cDNA were within or without the claims. That assertion cannot be agreed with.

The claims here assert a length for the cDNA in question and workers certainly know how to determine that length. The specification here teaches how one can assess whether the recited cytoplasmic mRNA is present in the cytoplasm of the tissues recited. Indeed, the figures show exemplary Northern blot hybridizations. (See for example, Figures 1A, 4A, 7A and 8A.) Assays for neuroactivity are provided throughout the specification such as at page 43, lines 5-15 and page 44, lines 15-34, as well as in several figures.

Thus, again, all that is needed is laid out for the skilled worker. That worker can readily ascertain whether infringement is present or not.

The Final Action also relied on In re Steel et al., 134 USPQ 292 (CCPA 1962) for the proposition that claims may be too indefinite to be examined as to prior art. That holding is not disagreed with, although its application here is.

Thus, the meaning of the words of the claims has been previously discussed and no contrary specifics have been asserted in the Action. As was noted before, breadth is not indefiniteness. Indeed, those skilled in this art knew and understood what is meant by the words of these claims in that the inventor's papers that are substantially completely present in this specification have been cited and relied-on 280 times by

those skilled workers. It is submitted that such "non-assertive conduct" is more than enough evidence of the definiteness of these claims. This rejection should again be reversed.

It is finally noted that the undersigned's firm has relocated to the address shown below. Counsel's new phone and fax numbers are also noted below. A separate change of address paper is enclosed with this APPELLANT'S BRIEF ON APPEAL TO expedite the appropriate change in mailing address of counsel.

Three copies of this Appellant's Brief on Appeal and the fee therefor are enclosed.

Respectfully submitted,

By _____
Edward P. Gamson, Reg. No. 29,381

Enclosures
Appendix I (Claims on Appeal)
Change of Address (in triplicate)
Fee

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CERTIFICATE OF MAILING

I hereby certify that this APPELLANT'S BRIEF ON APPEAL, in triplicate, together with the Brief fee, is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on December 11, 1995.

_____
Edward P. Gamson

APPENDIX I - CLAIMS ON APPEAL

26. Isolated and purified DNA having about 500 to about 1800 nucleotide bases that is complementary to cytoplasmic messenger RNA of a mammal that is present in brain cells but not in the cells of the liver, kidney, gut, lung, heart or skeletal muscle of the same species, said messenger RNA encoding a neuroactive proteinoid.

27. The DNA of claim 26 that is double stranded.

28. The DNA of claim 26 whose complementary messenger RNA has a number average of 160-10,000 nucleotide bases.

29. Isolated and purified double stranded DNA having about 500 to about 1800 nucleotide base pairs that is complementary to mammalian cytoplasmic messenger RNA, said messenger RNA (a) having a number average of 160-10,000 nucleotide bases, (b) being present in brain cells but not in the cells of the liver, kidney, gut, lung, heart or skeletal muscle of the same species, and (c) encoding a neuroactive proteinoid.

30. The DNA of claim 29 whose complementary messenger RNA contains 1600-4000 nucleotide bases.

32. Isolated and purified mammalian messenger RNA, said RNA:

(a) being present in brain cells but not in the cells of the liver, kidney, gut, lungs, heart or skeletal muscle of the same species;

(b) encoding a neuroactive proteinoid;

(c) having a number average of 160-10,000 nucleotide bases; and

(d) being polyadenylated.

33. The RNA of claim 32 that contains 1600-4000 nucleotide bases.